DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

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The Overdose Crisis: Interagency Proposal to Combat Illicit Fentanyl-Related Substances

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Chairwoman Eshoo, Ranking Member Guthrie, and members of the House Energy and Commerce Subcommittee on Health, thank you for inviting the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), to participate in this hearing. NIDA's mission is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health. I'm pleased to speak with you today about the importance of advancing research on fentanyl-related substances.

Fentanyl is a powerful synthetic opioid that is approximately 100 times more potent than morphine.[1] U.S. Food and Drug Administration (FDA)-approved fentanyl products are analgesics used medically during surgery, for treating post-surgical pain, and managing pain in opioid-tolerant patients. However, fentanyl and fentanyl-related substances are also made and distributed illegally; it is illicitly-manufactured fentanyl, fentanyl related substances, and other synthetic opioids that are driving the sharp rise in overdose deaths in the United States. Provisional data from the Centers for Disease Control and Prevention (CDC) show that drug overdose deaths exceeded 100,000 from April 2020 to April 2021, a staggering 28.5 percent increase over the previous year and the highest number ever recorded in a 12-month period.[2] Overdose deaths involving synthetic opioids—primarily illicit fentanyl and its analogs—increased by 55 percent in 2020.[3] Many of these deaths also involved other drugs, such as methamphetamine and cocaine, with which fentanyl-related substances may be mixed—often without the knowledge of the people who take them.

Research on Fentanyl and Fentanyl-Related Substances

With fentanyl and fentanyl-related substances driving the overdose crisis, research on these substances must be part of the solution. Indeed, research on these drugs is important for elucidating how they exert their adverse effects on the body and for developing treatments for fentanyl dependence, addiction, and overdose, among other conditions. This work is particularly important in light of reports that current medications for opioid use disorder and overdose may not be as effective when used against fentanyl. For example, there are reports that fentanyl overdoses may require additional naloxone doses to prevent "renarcotization" and that naloxone is not effective in reversing the fentanyl-induced chest wall and airway rigidity that contributes to fatal overdose.[4] There are also reports that people who use fentanyl may require higher buprenorphine doses for treatment induction,[5] and that more severe and prolonged neonatal abstinence syndrome may occur following fentanyl exposure.

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7233332/
[2] https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm
[3] https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm
[4] https://jpet.aspetjournals.org/content/371/2/453.long
[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6585403/

Recognizing the urgent need for research on fentanyl and fentanyl-related substances, NIDA issued a Notice of Special Interest[6] and a targeted request for applications[7] soliciting research on fentanyl and fentanyl-related substances. The applications funded under these announcements will add to the dozens of studies NIDA is already supporting on these drugs. For example, NIDA-supported researchers are currently using fentanyl-related substances to develop:

- accurate and easy-to-use fentanyl test strips that can detect illicit fentanyl and fentanyl-related substances in drug samples,[8]
- monoclonal antibodies to prevent fentanyl-related substances, including carfentanil, alfentanil, sufentanil and acetylfentanil, from exerting their effects on the brain, leading to respiratory depression, overdose, and death,[9] and
- small molecule "sequestrants" that can rapidly reverse fentanyl-related substance overdoses by binding to fentanyl molecules in the blood and accelerating their removal from the body through urine.[10]

Challenges to Conducting Research with Schedule I Substances

Fentanyl and fentanyl-related substances are regulated under the Controlled Substances Act (CSA), and researchers who want to work with them must obtain a research registration from the Drug Enforcement Administration (DEA). While fentanyl is a Schedule II substance, in part because it is an active ingredient in FDA-approved medical products, the vast majority of fentanyl-related substances, defined as a class by their chemical structure, are temporarily controlled under CSA Schedule I, the most restrictive schedule. The Biden-Harris Administration proposes to make permanent, and place in statute, this class-wide scheduling. Importantly, however, the Administration's proposal, which was developed by an interagency group including the White House Office of National Drug Control Policy (ONDCP), the Department of Health and Human Services (HHS), and the Department of Justice (DOJ), also includes provisions to facilitate research on fentanyl-related substances and other Schedule I drugs. The Administration is proposing these provisions to address the research community's concerns that obtaining a registration to conduct research with Schedule I substances can involve administrative challenges that sometimes impact the progress of research necessary to understand and ameliorate the public health effects posed by fentanyl-related substances.

[6] https://grants.nih.gov/grants/guide/notice-files/NOT-DA-21-032.html
[7] https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-22-022.html

[8] https://reporter.nih.gov/search/GnrlRG16BUqgjUSV1N0Q_g/project-details/10133593
[9] https://reporter.nih.gov/project-details/10227130
[10] https://reporter.nih.gov/project-details/10390959

Even experienced researchers have reported that obtaining a new Schedule I registration, adding new substances to an existing registration, or getting approval for research protocol changes is time consuming. Unlike for Schedule II through V substances, new and amended Schedule I applications are referred by the DEA to the HHS for a review of the protocol and a determination of the qualifications and competency of the investigator. This review is often in addition to other reviews of the proposed research and investigator, such as the federal grant review process, the FDA Investigational New Drug (IND) application review process, and Institutional Review Board and Institutional Animal Care and Use Committee reviews. Establishing the security infrastructure needed to conduct Schedule I research can be expensive and may need to be duplicated for each registrant working within a single research department. Researchers have also reported that there is a lack of clarity in some of the registration requirements and variability in their interpretation, which complicates and adds time to the process. For example, researchers report inconsistency in the guidance they have received on whether one individual can work under the registration of another, whether separate registrations are needed for each of an investigator's research sites within the same campus, whether a manufacturing registration is needed to create final dosage formulations for research purposes, among other issues. Researchers have reported that sometimes these challenges impact Schedule I research and deter or prevent scientists from pursuing this critical work.

Removing Fentanyl-Related Substances with No or Low Abuse Liability from Schedule I

One of the ways by which the Administration proposes to facilitate research with fentanyl-related substances scheduled as a class is by establishing an expeditious process for descheduling or rescheduling those subsequently found to have no or relatively low abuse potential. This is important because class-wide scheduling of fentanyl-related substances bypasses the substance-by-substance analysis of a compound's abuse potential that is conducted when substances are scheduled via the typical administrative process. Instead, fentanyl-related substance scheduling would be based on chemical structure alone, resulting in the potential placement of thousands of compounds—including those not yet discovered—into Schedule I. Some of these compounds may not have the "high potential for abuse" that is a criterion for Schedule I placement. Indeed, scheduling based on chemical structure alone theoretically could result in the placement into Schedule I of substances with no abuse potential, including substances that could be developed for treating opioid use disorder, fentanyl overdose, pain, and other medical conditions. This is because simple changes to a chemical's structure can impart substantial changes in its activity; therefore, it is not possible to definitively predict a substance's abuse liability from its structure alone.

A recent paper published by Comer and colleagues[11] demonstrates this. They note that benzylideneoxymorphone, though structurally related to the potent opioid oxymorphone, has very low potential for abuse. Likewise, mirfentanil, a substance that meets the structural definition of a fentanyl-related substance, has been shown to have low abuse liability. They also point to AT-202, a fentanyl-related substance studied as a potential analgesic that does not show the same adverse effects profile as other compounds that activate mu opioid receptors and is expected to possess only low abuse liability.

Although the CSA does have a framework for de-scheduling and rescheduling substances, that process is time-consuming in that it involves the same eight-factor analysis required for administratively scheduling a substance. The expedited process proposed by the Administration (and described in more detail in Section 5 of the proposed legislation, "Removal from Schedule I of Fentanyl-Related Substances") would only apply to fentanyl-related substances placed in Schedule I as a class without a substance-by-substance determination of their potential for abuse. It would require HHS to consider one of the eight factors (the scientific evidence of the substance's pharmacological effect, including its abuse potential), and, to the extent evidence exists, three other factors from the set of eight. It would also identify a three-part assessment of the substance's mu opioid activity and establish that performing that assessment would suffice to constitute consideration of the substance's pharmacological effect. If this analysis leads HHS to conclude that the substance had less potential for abuse than substances in Schedule V (the least restrictive schedule under the CSA), the Department of Justice (DOJ) would be required to remove the substance from the schedules within 90 days. If the process leads HHS to conclude that the substance has a potential for abuse less than that of substances in schedules I and II, the DOJ would be required, within the same time period, to remove the substance from schedule I and reschedule it in schedule III.

Streamlining the Schedule I Research Registration Process

Just as it is important to have a process for expeditiously removing substances that do not have high abuse liability from Schedule I of the CSA, it is equally important to facilitate research on the substances that remain in Schedule I, as is expected to be the case for the vast majority of fentanyl-related substances. The Administration proposes to do this by streamlining and clarifying the Schedule I research registration process as described in Section 7 of the proposed legislation, "Registration Requirements Related to Research," and summarized below.

(a) **ALTERNATIVE REGISTRATION PROCESS FOR SCHEDULE I RESEARCH.** The Administration's proposal creates an alternative registration process for Schedule I research funded by HHS or the Department of Veterans Affairs (VA), or conducted under an IND. Under

[11] Comer SD, Pravetoni M, Coop A, Baumann MH, and Cunningham CW. Potential unintended consequences of class-wide drug scheduling based on chemical structure: A cautionary tale for fentanyl-related compounds. *Drug and Alcohol Dependence.* Vol. 221, 1 April 2021.

the proposed process, researchers would submit a notice to DOJ containing: the identity of the substance to be used; the quantity of the substance to be used; demonstration that the research is funded by HHS or by the VA, or is conducted under an Investigational New Drug (IND); and demonstration that the researcher is allowed to do the research under the law of the state where it will be conducted. If the researcher already holds a schedule I or II research registration he or she may commence the research 30 days after sending the notice described above—without waiting for a notification of approval from the DOJ. If the researcher does not already have such a registration, that notice suffices to constitute the application, and DOJ must either grant the registration or issue a show-cause order denying the registration within 45 days.

This proposal would align the Schedule I research registration process more closely with the process for obtaining a research registration for Schedule II substances, which are defined as having the same "high potential for abuse" as Schedule I substances and include fentanyl, methamphetamine, and cocaine, among other drugs. Specifically, Schedule I applications would not be referred to HHS for a review of the protocol and determination of the qualifications of the investigator. Likewise, it would no longer be necessary for investigators to submit an amended application notifying the DOJ of research protocol changes as long as those changes do not modify the quantity of the substance used. Removing the application referral and review steps—consistent with the process currently in place for research with Schedule II substances—will expedite the registration process without sacrificing federal oversight of the research, which will already have been reviewed as part of the HHS or VA funding process, and/or the FDA IND application process. Allowing current Schedule I or II registrants to proceed with the research without an affirmative decision by the DOJ will further expedite the process and hence the research. Moreover, these changes are not expected to have any impact on substance diversion, because the current Schedule I security and inventory controls would continue to apply.

(b) **SEPARATE REGISTRATIONS NOT REQUIRED FOR ADDITIONAL RESEARCHER IN SAME INSTITUTION.** Currently, under the CSA every individual using a schedule I substance in research must have a registration to do so unless subject to an applicable exception. The CSA makes an exception for agents or employees of the individual who is registered. There are instances, however, when research in an institution is performed by individuals who are agents or employees of the institution, but not technically the agents or employees of the individual who holds the registration. This subsection would make clear that, under certain conditions, those individuals may perform research without being separately registered. This expansion is especially important where the registrant and the other researchers are a research team, but the other members are not necessarily agents or employees of the registrant. However, it also applies in situations in which the researchers are not working as an investigative team. For example, this expansion clarifies that it is permissible for a senior investigator in a research department to hold a registration under which other independent researchers in the department work. The registered researcher would have to inform DOJ of the identities of all such individuals, would have to authorize them to participate, and would have to affirm that

any illicit or unapproved acts involving controlled substances by such individuals would be attributed to the registered researcher for the purpose of determining whether the researcher should continue to be registered. Since such acts inconsistent with a registrant's duties could imperil the registrant's registration, he/she would have a strong incentive to ensure that such acts do not occur.

(c) **SINGLE REGISTRATION FOR RELATED RESEARCH SITES.** Currently, the CSA requires a separate registration for each principal location where the registrant works with schedule I substances. Under the Administration's proposal, a single research registration would cover use of multiple locations for the performance of the research or the storage of the substances, as long as all the sites are under the control of the same institution and are in the same city or county, and as long as the researcher notifies DOJ of each such site before the site is used to conduct the research or to store the substances. The subsection would specifically authorize DOJ regulations to ensure that effective controls against diversion of substances are in place at the additional research sites.

(d) **NEW INSPECTION NOT REQUIRED IN CERTAIN SITUATIONS.** This subsection would make clear that, if a researcher has a registration to perform research with one controlled substance and applies to research another substance controlled under the same schedule or under a less restrictive schedule, a new inspection of the research site is not required. Current law does not mandate a new inspection in that circumstance, but staff implementing the statute have sometimes presumed that a new inspection is required; this provision would make clear that a new inspection is not required. This provision, however, does not prevent DOJ from conducting any inspections deemed necessary to ensure that a registrant maintains effective controls against diversion.

(e) **CONTINUATION OF RESEARCH ON SUBSTANCES NEWLY ADDED TO SCHEDULE I**. This subsection would allow researchers who already have schedule I research registrations to continue to conduct research with newly scheduled (Schedule I) substances on which they have already been conducting research. Under this subsection, such researchers would have to apply within 90 days for a registration (or a modification of the existing registration) to work on the new substance, but the research could continue uninterrupted until the application is withdrawn or until DOJ issues a show-cause order proposing to deny the application.

(f) **TREATMENT OF CERTAIN MANUFACTURING ACTIVITIES AS COINCIDENT TO RESEARCH.** Under the CSA, manufacturing registrations and research registrations are separate, although researchers may conduct limited manufacturing as a coincident activity of their research registration without obtaining a manufacturing registration under certain circumstances. This subsection would make clear that a researcher would not be required to obtain a separate manufacturing registration if the manufactured quantities are small, if the manufacturing is done for purposes of the research, and if the researcher notifies DOJ of the

manufacturing activities and the quantities of the substance that will be involved. This authority specifically includes creating different forms of the substance consistent with the research, and dosage for development studies performed in order to apply to FDA for an IND exemption. The subsection does not provide authority to grow marijuana.

(g) **TRANSPARENCY REGARDING SPECIAL PROCEDURES**. The DOJ occasionally determines, with respect to particular controlled substances, to apply special processes, or special criteria, to applications for registrations to research those substances -- processes or criteria that are consistent with the law but are not necessarily applied to other substances in the same schedule. Registrants are not always aware of which substances are on this "Code H" list, or what special processes or criteria are required for these substances. This subsection would require DOJ to make public which substances are on the list, what special processes or criteria apply to them, and how those processes or criteria differ from those applying to other substances on the same schedule.

Conclusion

Fentanyl-related substances are driving the U.S. overdose epidemic, resulting in an unprecedented loss of life. Research to develop treatments for opioid overdose and opioid use disorder is more urgent than ever. By making meaningful changes to the Schedule I research registration process, the Administration's proposal would facilitate research on fentanyl-related substances and all Schedule I drugs and, in doing so, expedite the development of solutions to the overdose epidemic. Thank you for the opportunity to address this issue. I am happy to answer your questions.